

Clinical Evaluation of First In Vivo mRNA-LNP TROP2-Directed CAR, MT-302, in Solid Tumours

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Background

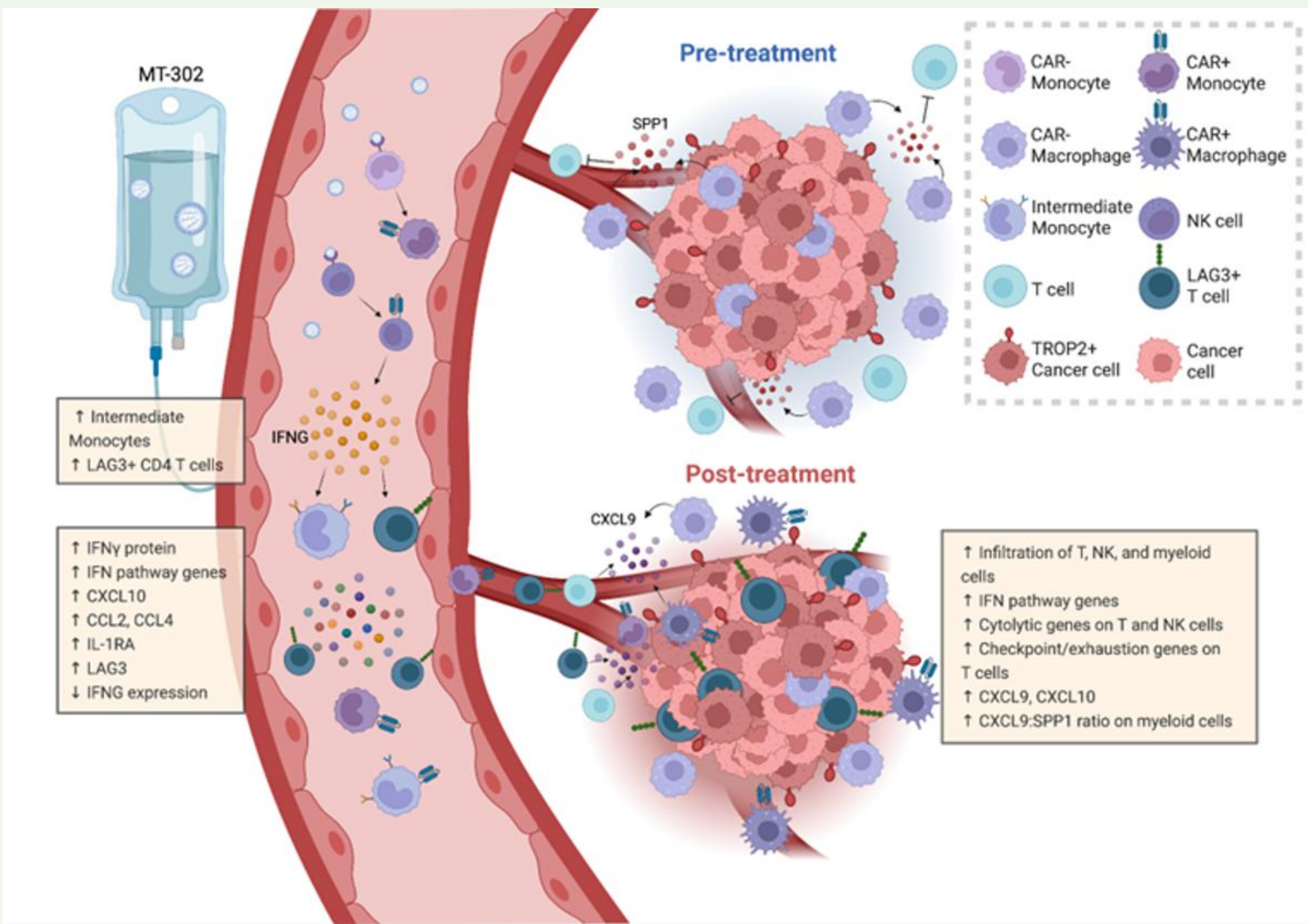
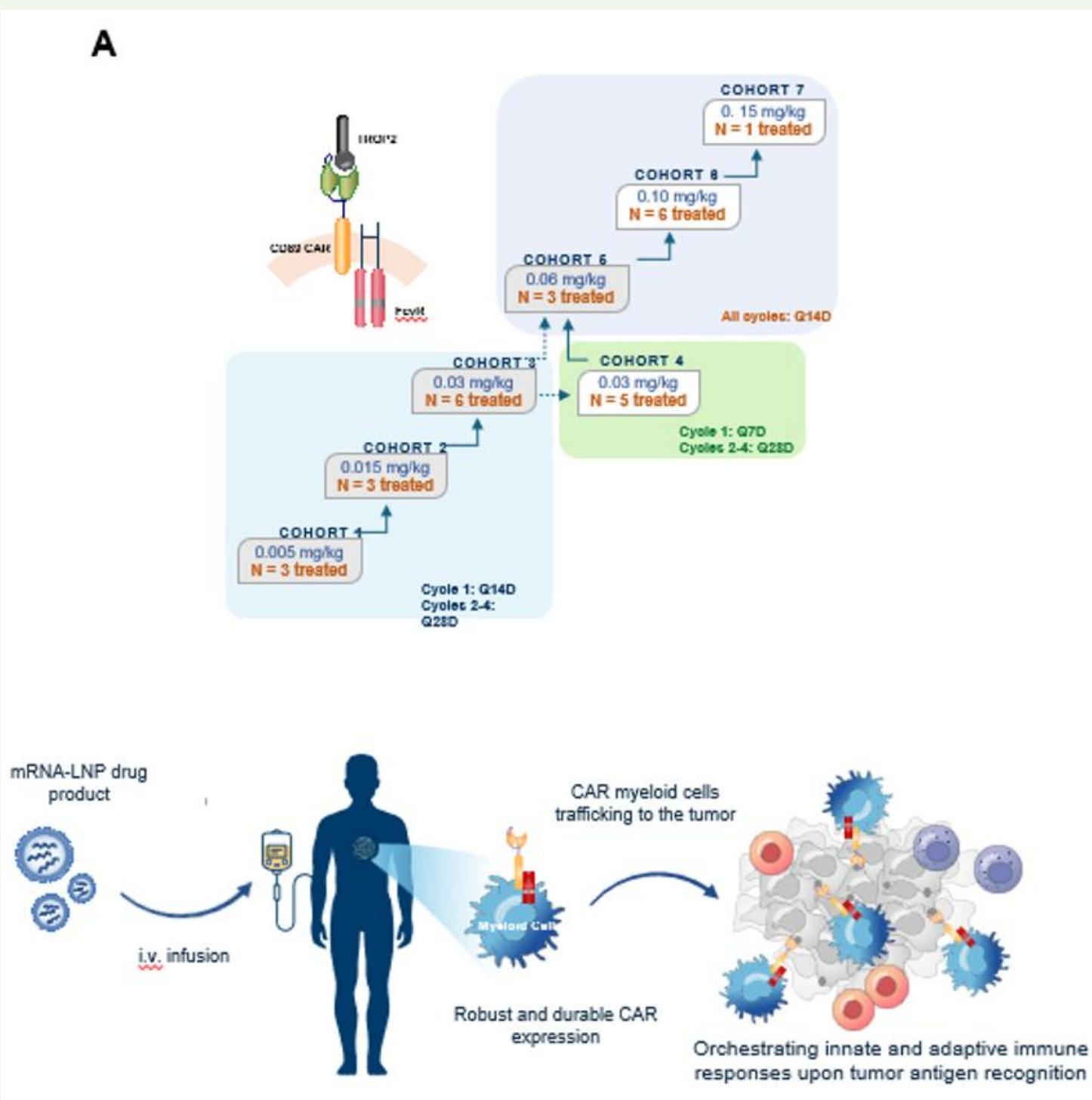
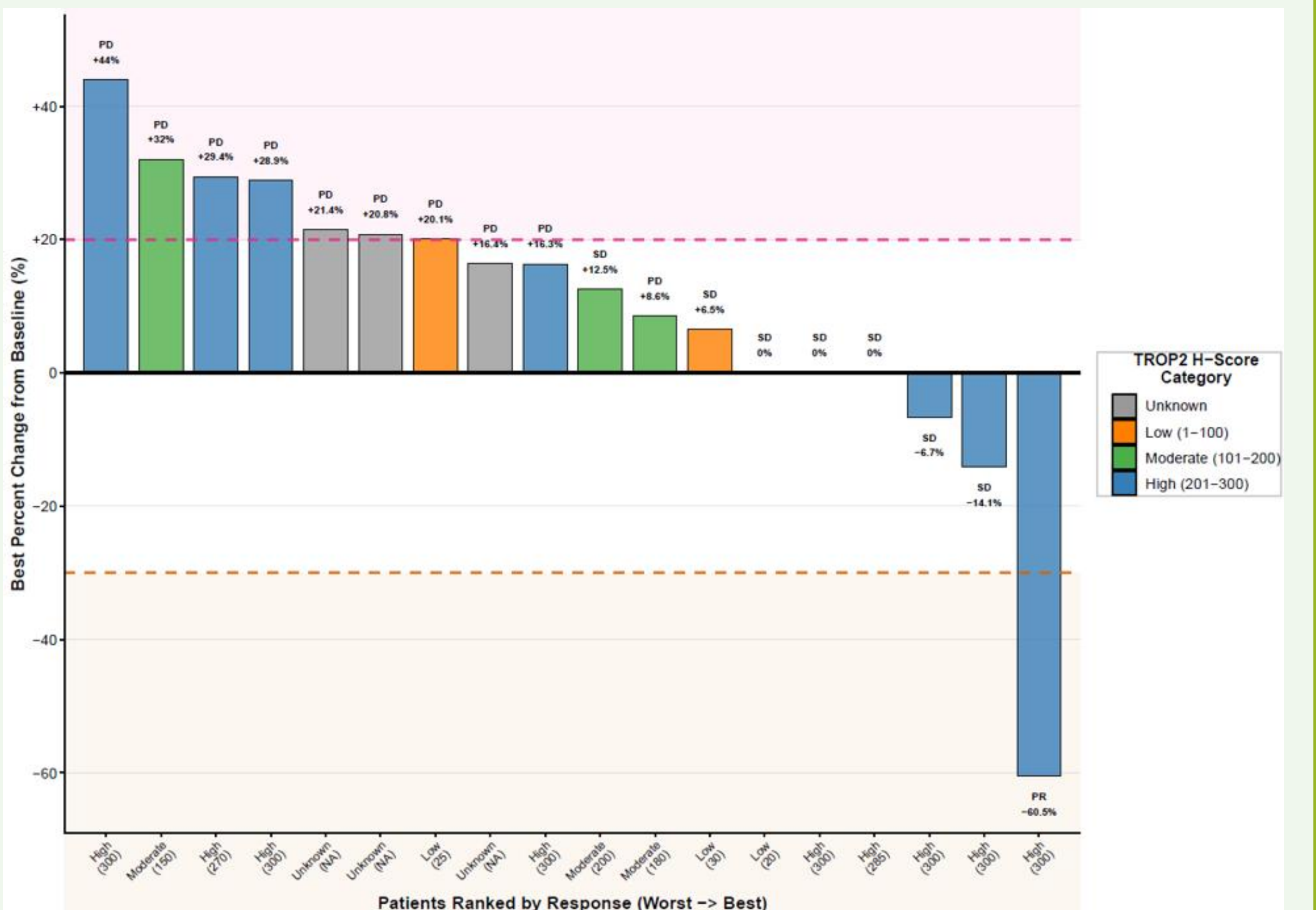
Chimeric antigen receptor (CAR) T-cell therapies have transformed the treatment of haematological malignancies but show limited efficacy in most solid tumours. Poor T-cell infiltration, heterogeneous antigen expression and an immunosuppressive tumour microenvironment (TME) dominated by myeloid cells collectively restrict durable responses. Tumour-associated macrophages (TAMs), monocytes and dendritic cells are the most abundant immune population in many solid tumours, where they control antigen presentation, cytokine gradients and T-cell access to the tumour bed. Reprogramming these cells to recognize tumour cells and shift from an immunosuppressive to a pro-inflammatory phenotype is a potentially therapeutic strategy in solid tumours. Interferon- γ (IFN γ) is a mediator of this conversion: it triggers chemokine production, MHC upregulation, and polarises TAMs to have anti-tumour activities. The high-affinity IgA receptor CD89 (Fc α RI) is expressed predominantly on myeloid cells, where it activates innate effector functions such as phagocytosis, cytokine production, and antigen presentation. Because CD89-based immunotherapies elicit antitumour responses in preclinical lung and colorectal cancer models, and CD89 is also present on a subset of human NK cells, we sought to exploit these pathways. Here, we report the first in human results of MT-302, an intravenously administered mRNA-LNP encoding a TROP2-directed, CD89-based CAR. MT-302 selectively programs circulating monocytes and NK cells *in vivo* by leveraging CD89's natural dependence on the FcR γ common chain. Because the truncated CD89 domain of the encoded CAR must associate with this endogenous adapter to stabilize and activate on the cell surface, functional expression is strictly restricted to FcR γ -expressing immune cells. This strategy bypasses *ex vivo* cell manufacturing, allowing for repeated dosing to sustain innate immune cell activity against TROP2-expressing cancers.

Methods

A first-in-human, open-label, phase 1 dose-escalation study of MT-302 was conducted at six sites in Australia. Patients with advanced TROP2-enriched epithelial tumours (NCT05969041) were enrolled, and MT-302 was administered by intravenous infusion across seven dose-escalation cohorts spanning six dose levels (0.005–0.15 mg kg⁻¹; cohorts 3 and 4 both evaluated 0.03 mg kg⁻¹ on different schedules), in which a Bayesian Optimal Interval (BOIN) dose-escalation design^{119,20} informed the safety review committee decisions. The initial dosing schedule was every two weeks for 3 doses (weekly for cohort 4) followed by monthly maintenance, but was amended to continue dosing every two weeks on the basis of the pharmacokinetic profile.

Results

Twenty-seven heavily pretreated patients with advanced epithelial cancers received biweekly intravenous infusions of MT-302 (0.005–0.15 mg kg⁻¹). Repeat dosing was feasible and safe (mean 4 infusions; maximum 20), with limited RNA-associated reactogenicity and no grade ≥ 3 cytokine release syndrome. In paired blood samples and tumour biopsies, MT-302 demonstrated evidence of induced CAR expression in myeloid and natural killer cells, increased effector cytokine and chemokine production, and remodelled the tumour microenvironment through pro-inflammatory macrophage polarisation, enhanced antigen presentation and T-cell infiltration demonstrated by spatial transcriptomics. One patient with hormone receptor-positive breast cancer achieved a confirmed partial response and remained on therapy for 20 infusions.



Conclusion

MT-302 provides first-in-human evidence that systemic mRNA-LNP delivery can programme innate immune cells *in vivo* to drive antigen-dependent immune activation and remodel the human tumour microenvironment, establishing a foundation for biomarker-driven combination strategies aimed at converting immune remodelling into durable antitumour responses. These results establish the ability to repeat dose mRNA CAR MT-302 in humans and proof of mechanism for myeloid programming in solid tumours.